REMARKS

I. Support for the Amendments

Claims 1-21 were originally in the application. Claims 6-21 were canceled without prejudice or disclaimer of any subject matter.

Claims 1-5 and 22 are presently in the application. Claims 1 and 4 have been amended, and new claim 22 has been added. No new matter has been added.

Support for amended claims 1 and 4 can be found in the original specification and claims. Additional support for amended claim 1 and new claim 22 can be found, e.g., on page 3, lines 3-22; on page 4, lines 1-4; from page 5, line 26, to page 6, line 7; on page 6, lines 16-20; from page 6, line 23, to page 7, line 25; on page 8 line 3-6; in Figures 1-3; and in the Examples. Additional support for amended claim 4 can be found, e.g., on page 4, lines 9-10; on page 5, lines 5-7; in Figure 6; and in the Examples.

II. Status of the Claims

Claims 1-21 were originally in the application. Claims 1-21 were subject to an election/restriction requirement, and claims 1-5 were elected with traverse. Claims 6-21 were canceled without prejudice or disclaimer of any subject matter. New claim 22 has been added. Claims 1-5 and 22 are presently in the application.

III. The Examiner's Detailed Action Remarks are Addressed

On page 2 of the Office Action, the Examiner states, in part:

A third non-responsive letter was sent on 6-25-03 because the SEQ ID NOs in Table 1 were deleted. Applicants responded on 9-10-03 by requesting withdrawal of the request to amend Table 1. While the last response by applicants is not considered "responsive," the following office action is set forth to expedite prosecution. (The response is non-responsive because amendments cannot be withdrawn. To add the SEQ ID NOs back into the Table and to change the amino acid sequence of H12 back to the original sequence, applicants must replace the pending Table with a corrected Table using the proper format for amending the specification.) (Page 2.)

Applicants have amended Table 1 in the specification in accordance with the Examiner's remarks and respectfully request the Examiner to amend the specification. Applicants respectfully submit that the amendments to Table 1 address the Examiner's remarks.

In addition, Applicants wish to thank the Examiner for entering the after-final amendment of 16 January 2003.

IV. The Examiner's Remarks Concerning the Specification are Addressed

On page 3 of the Office Action, the Examiner states, in part:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **The sequences on pg 9, Table 1, do not have SEQ ID NO.** Applicants must file a "Sequence Listing" accompanied by directions to enter the listing into the specification as an amendment. Applicant also must provide statements regarding sameness and new matter with regards to the CRF and the "Sequence Listing." Failure to fully comply with the sequence rules in response to the instant office action will be considered non-responsive.

Please make sure that any amendments to the amino acid sequence of H12 in Table 1 correlates to the amino acid sequence of SEQ ID NO:51 in the pending computer readable format and paper listing. (Page 3; emphasis in original.)

Applicants request the entry of the changes in the specification requested above. It is believed that no new matter has been added by virtue of the amendments made to the specification.

Applicants submit herewith a revised Sequence Listing, pages 1-21, to include as a revised sequence listing as part of this Application. The pages of the revised Sequence Listing are provided in both paginated and unpaginated format for the Examiner's convenience. Please enter the revised Sequence Listing and renumber the pages of the Sequence Listing along with those of the claims and the abstract accordingly.

Further enclosed is a computer readable copy of the above-mentioned copy of the Sequence Listing. That copy is the same as the copy of the Sequence Listing.

Also enclosed is a Statement in Support of Filing and Submissions in Accordance with 37 CFR 1.821-1.825, which declares that the content of the paper and the computer readable copies of the Sequence Listing submitted in accordance with 37 CFR 1.821 (c) and (e), respectively, are the same and that the submission, filed in accordance with 37 CFR 1.821 (g) does not introduce new matter.

The replacement Sequence Listing, and amendments to the specification, including Table 1, are submitted to make them consistent with one another and to provide sequence identifier numbers. Support for the present amendments can be found throughout the application including the claims and drawings as filed originally. No new matter has been added by virtue of the amendments.

Applicants respectfully submit that the replacement Sequence Listing and the amendments to the specification hereby address the Examiner's concerns and place the application in condition for allowance.

V. Rejection of Claims 1-5 Under 35 U.S.C. §112, Second Paragraph, is Traversed, but Accommodated

Applicants thank the Examiner for withdrawing the rejection of claims 1-5 under 35 U.S.C. §112, first paragraph.

However, the Examiner has rejected claims 1-5 under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

The Examiner alleges:

> Claim 1 is indefinite because the phrase "preparea nucleic acid sequence encoding at least one of each of the variable regions of the α and β chains" as newly amended is indefinite. The claim fails to set forth the structure of the nucleic acid sequence prepared by stating it comprises a nucleic acid sequence of an α chain TCR and a nucleic acid sequence of a β chain TCR. As written, it appears the claim may encompass a nucleic acid molecule encoding each of the possible a chains and each of the possible β chains.
>
> Claim 1 is indefinite because "said nucleic acid molecules" (line 9) lacks antecedent basis. Only the phrase "nucleic acid molecule" occurs prior to line 9. in addition, the "molecule" in line 1 does not encode anything as in line 9; the molecule in line 1 comprises a sequence encoding at least one variable region.
>
> Claim 1 remains indefinite because the phrase "recovering said HLA restricted CTL, which contain said nucleic acid molecules encoding at least one of each of the variable regions of the α and β chains" is unclear. The claim fails to set forth the structure of the CTL recovered by stating they comprises a nucleic acid sequence of a variable TCR α chain and a nucleic acid sequence of a variable TCR β chain. As written, the language used is confusing because it refers back to "said nucleic acid molecules" which is also unclear (see above). It is also unclear whether the claim encompasses recovering a CTL having a nucleic acid sequence encoding each of the possible α chains and each of the possible β chains.
>
> Claim 1 is indefinite because it is unclear if both the α and β chains are cloned/amplified in lines 11-12, or if only one or the other is cloned/amplified. In fact, it is unclear that any part of the variable region is cloned/amplified because a non-variable region sequence in the nucleic acid molecule may be cloned/amplified. As written, any portion of the molecule may be cloned or amplified, including non-variable regions sequences. The claim does not clearly set forth that a variable TCR α and β chain are cloned/amplified.

Claim 1 is indefinite because it is unclear if both the α and β chains are recovered in line 13. The phrase "TCR receptor-encoding nucleic acid molecules" lacks antecedent basis. As written, any portion of the molecule may be cloned or amplified, including non-variable regions sequences. Therefore, it is unclear that both the α and β chains would be recovered. The claim does not clearly set forth that a variable TCR α and β chain fusion protein is recovered.

Claim 1 is indefinite because it is unclear to what "fusing the recovered nucleic acid molecules" in lines 14-15 refers. The phrase "the nucleic acid molecule[s]" occurs on line 1, 9, 11 and 13. It is unclear whether the claim is limited to an α chain fused to β chain, or if any two chains recovered in line 13 are fused together are encompassed by the claim. It is unclear whether any variable chain fused together with another nucleic acid sequence is encompassed by the claimed. The claim does not clearly set forth the nucleic acid sequences being fused together.

Claim 1 is indefinite because the metes and bounds of what applicants consider a single chain TCR cannot be determined (line 15). It is unclear if a "single chain TCR" encompasses any β chain by itself or if the phrase is limited to a fusion protein of a TCR α and β variable region.

Claims 4 remains indefinite because the "cloning or amplifying step" in claim 1 does not "comprise" anything, so it cannot "further comprise" anything. (Pages 5-7; emphasis in original.)

As noted in the Amendment filed 26 June 2002,

With respect to claim 1..., the featured nucleic acid encodes at least one of each of the variable regions of the α and β chains. That is, the nucleic acid must include one of the α chain variable regions and one of the β chain variable regions. (Amendment (6/26/02), page 4.)

The same remarks continue to apply to claim 1, both before and after the present amendment. Claims 2-5 are dependent on claim 1.

While Applicants respectfully disagree with each position of the Examiner, in order to further prosecution in a timely manner, Applicants submit that the amendments to claims 1 and 4 address all of the points made by the Examiner, *supra*, and place claims 1-5 in a condition for allowance.

VI. Rejection of Claims 1-5 Under 35 U.S.C. §103(a) is Traversed

The Examiner has rejected claims 1-5 under 35 U.S.C. §103(a) as being unpatentable for obviousness over Man (J. Immunol. 153: 4458-4467 (1994)) in view of Cole (FASEB J. 9: A801 (April 1995)). Applicants respectfully disagree with the rejection for reasons already of record. Applicants further disagree with the Office in view of the present submission.

The Examiner alleges:

> Man taught immunizing transgenic mice expressing HLA-A2.1 with $M1_{(58-66)}$ (influenza antigen), isolating CTL from the mice that lyse the M1, amplifying DNA encoding the α and β chain of the M1-specific TCR by PCR (pg 4459, col. 1, "influenza-specific CTL from HLA-A2.1 transgenic mice"; pg 4459, col. 2, "PCR amplification and sequencing of TCR α and β-chain cDNA). The primers used by Man were mouse α and β TCR-specific primers Vβ8, Vβ5 and Vβ6, which are the primers Vβ8.1, Vβ8.2, Vβ8.3, Vβ5.1 and Vβ6 primers in Fig. 6. The Man did not teach isolating TAA-specific TCR from the mice. However, Cole taught isolating MART-1-specific, HLA-A2 restricted CTL and the α and α chains of TCR recognizing MART-1 from the CTL (see entire abstract). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of isolating TCR genes from transgenic mice taught by Man to obtain TCR genes specific for the MART-1 antigen. One of ordinary skill would have been motivated to replace the M1 antigen with the MART-1 antigen to obtain MART-1 specific TCR *in vivo*.
>
> Man taught "fusing the recovered nucleic acid molecules together to prepare the isolated nucleic acid molecule" as newly amended because the recovered nucleic acid molecules were fused together with the PBKS- vector. The claim does not require recovering a nucleic acid sequence encoding an α chain and a β chain. Nor does it require fusing a nucleic acid sequence encoding an α chain to a nucleic acid sequence encoding β chain. (Pages 7-8.)

Applicants respectfully disagree with the Examiner's comments and traverse the obviousness rejection.

As noted in the Amendment filed June 26, 2002, claim 1 had previously been amended to include a further step in which the receptor-encoding nucleic acid molecules are fused together. The recited nucleic acid molecule thus encodes a one chain non-human T-cell receptor (TCR). Additionally, the encoded TCR includes at least one of the variable regions of the α chain and at least one of the variable regions of the β chain. Presently amended claim 1 likewise recites a nucleic acid molecule encoding a one-chain non-human TCR including at least one of the

variable regions of the α chain and at least one of the variable regions of the β chain. These encoded fusion proteins retain HLA restriction and antigen specificity characteristics of the CTL (see page 5 of the specification).

Applicants' method of making such a nucleic acid is not taught or suggested by the cited references taken either individually or together with the other references of record.

For instance, the cited Man reference is understood to disclose methods by which multiple nucleic acids are used to make two-chain molecules. In contrast, the present invention provides methods for fusing nucleic acids to make a one-chain molecule. Moreover, the methods of Man rely on PCR amplification of cDNA using oligonucleotide primers. As described in Man for both the TCR Vα and Vβ chains (see p. 4459 of Man and reference 34 [Danska et al., J. Exp. Med. 172: 387 (1990) (previously cited in IDS, filed Oct. 30, 2003)]), PCR amplification was carried out with 5' primers specific to the second framework region of the V domain and antisense primers specific to the constant domain. The resulting PCR products encoded a fragment from the TCR α and β V-C regions, but lacked sequences encoding the 3' ends of the V regions, the first framework, CDR1, and a portion of the second framework. These truncated Vα and Vβ fragments would be expected to lack structural features necessary to retain HLA restriction and antigen specificity characteristics. While Man describes the fusion of recovered nucleic acid molecules together with the PBKS-vector for purposes of sequencing, Man does not describe fusion of at least one α chain and at least one β chain, nor does Man describe the PBKS-vector fusions as encoding a fusion protein capable of retaining antigenic specificity (see, e.g., preamble of claim 1). Moreover, the method of Man is further complicated by the fact that there are over 80 different Vα chains with little or no sequence homology at their 5' ends. This lack of homology prohibits the design of degenerate PCR primers, as in Man. Thus, a one of ordinary skill in the art at the time of the invention would not use the method taught by Man to isolate a nucleic acid molecules for providing a functional TCR fusion protein having at least one α chain and at least one β chain and capable of retaining antigenic specificity.

Cole fails to supply the deficiencies of Man, nor is there any suggestion in Cole or in Man to combine the methods of Cole with the methods of Man in order to teach or suggest the present invention.

Specifically, the Cole reference is relied on as providing methods for isolating MART-1-specific, HLA-A2-restricted CTL. As understood, the cited Cole reference describes the identification of TCR α and β variable genes from MART-1-specific, HLA-A2-restricted CTL clones. From the abstract, it is not clear whether the genes themselves were isolated, whether only portions of the sequences were identified (e.g., by amplification of local areas), or whether some alternative method (e.g., RNA hybridization) was used merely to identify, rather than actually isolate, the sequences. Cole is silent on the methods used to identify the TCR genes. Thus, it would have been impossible for one of ordinary skill in the art to rely on Cole, either alone or in combination with Man, to provide methods for isolating nucleic acid molecules for providing a functional TCR fusion protein having at least one α chain and at least one β chain and capable of retaining antigenic specificity.

The cited Man and Cole references do not teach or suggest any fusion step for making the claimed nucleic acid molecule of the present invention in order to join the sequences encoding the TCR variable region. Likewise, they neither teach nor suggest sequences encoding a Vα or Vβ protein retaining antigenic specificity.

Claims 2-5 are dependent on claim 1, and the same arguments apply to those claims.

Applicants respectfully submit that the present claims 1-5 fulfill the requirements of 35 U.S.C. §103(a) and request the Examiner's reconsideration of these claims accordingly.

VII. CONCLUSION

In view of the foregoing amendments and remarks, the present application is respectfully considered in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited.

It is believed that all outstanding rejections have been addressed by this submission and that all the claims are in condition for allowance. If discussion of any amendment or remark made herein would advance this important case to allowance, the Examiner is invited to call the undersigned as soon as convenient.

It is believed that no extension of time is required. If a petition for an additional extension of time is required, then the Examiner is requested to treat this as a conditional petition for an additional extension of time. Although it is not believed that any additional fee is required to consider this submission, the Commissioner is hereby authorized to charge our deposit account no. 04-1105 should any fee be deemed necessary.

Respectfully submitted,

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